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• REVIEW •

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Stem cell therapies and regenerative medicine in China

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Stem cells are the core of tissue repair and regeneration, and a promising cell source for novel therapies. In recent years, research into stem cell therapies has been particularly exciting in China. The remarkable advancements in basic stem cell research and clinically effective trials have led to fresh insights into regenerative medicine, such as treatments for sweat gland injury after burns, diabetes, and liver injury. High hopes have inspired numerous experimental and clinical trials. At the same time, government investment and policy support of research continues to increase markedly. However, numerous challenges must be overcome before novel stem cell therapies can achieve meaningful clinical outcomes.

stem cells, regenerative medicine, tissue engineering, clinical trial

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Regenerative medicine is a rapidly rising multidisciplinary field that aims to restore, maintain or enhance the function of tissues and organs. The continuing expansion of medical research and rapid increase of new medical technologies are believed to play important roles in the emerging field of regenerative medicine. With China's rapid economic growth and aging population, the healthcare burden of degenerative diseases, tumors, tissue and organ defects, and other age-related diseases has increased gradually. However, current therapeutic strategies either are limited by donor availability and immunological barriers or pertain to only a minor range of conditions. Moreover, such conditions are unlikely to be completely cured by current traditional treatments or drugs, and need restoration of tissue function through novel therapeutic approaches. For many incurable diseases and disorders of the aging population, innovative applications of tissue engineering and novel cell therapies derived from pluripotent and tissue-restricted stem cells represent major frontiers for the future [1].

1 Frontline innovations

Over the last 20 years, scientists and clinicians around the world have carried out numerous animal experiments and clinical trials of stem cells and achieved remarkable results. In 2005, the United States (US) Food and Drug Administration (FDA) approved an orphan drug product consisting of human stem cells (Prochymal, Osiris Pharmaceuticals, USA) for graft-versus-host disease in acute rejection treatment. Provacel™, the second product of this company Osiris Therapeutics Inc. for heart repair, has been evaluated in a phase I clinical study. Recently, its third product, Chondrogen™, has received FDA approval to begin a clinical phase I/II study to repair tissue damage and prevent knee arthritis. In 2011, the South Korean Food and Drug Administration approved the sale of Hearticellgram-AMI that was developed by FCB-Pharmicell Inc. for myocardial infarction treatment. It is also the first therapeutic stem cell drug approved for marketing by a government. This first indicates that therapeutic stem cells have been recognized as a drug for regenerative medicine, which may prompt a new era in

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stem cell development.

Stem cell therapy in China ranks at the forefront in the world. Because of policy support, China has made considerable progress in basic research of stem cells and attracted the most patients for stem cell treatment worldwide. Since 2002, for rapid and effective development, the Chinese government has provided abundant research funding, such as that from the National Basic Research Program of China, National High Technology Research and Development Program of China, and National Natural Science Foundation of China (NSFC), to support related research on stem cells. Hence, many scientists and clinicians have benefited from this funding and accomplished certain achievements [2]. Figure1 summarizes the approved projects and funding from the NSFC for stem cell-based research and trials, and the related articles published in Science Citation Index journals from 2008 to 2012. These achievements involved preclinical studies of stem cells and tissue engineering products for coronary heart diseases, diabetes, liver failure, sweat gland injury after burns, and other serious diseases, which establish a solid foundation for clinical application and industrialization of future products [3–8]. However, the therapeutic market for stem cell applications is not mature enough in China, resulting in a lack of large-scale market-oriented stem cell-based products. The Chinese government has recognized the seriousness of this problem. Therefore, the former Health Ministry halted all stem cell therapy in early 2012. Although therapeutic stem cells are controversial, the market is still growing rapidly. The reasons are as follows: (i) high expectations and unmet medical need, (ii) lack of strict supervision awareness, and (iii) relatively easy-to-master technology. In 2013, the Health and Family Planning Commission published "Regulations on cell clinical trials base construction" and another three documents, hoping to effectively take the monitoring responsibility. Recently, "management approach on stem cell clinical trials (on trial)" and "management approach on stem cell clinical trial research base (on trial)" have been proposed by the Stem Cell Expert Committee of China, and the relevant terms should drive rapid development of stem cell-based therapies in China.

2 Different types of stem cells for research and clinical trials

Before filing an investigational new stem cell for application, the applicant should be able to address the following questions: Does the donor pose a risk of transmitting infectious or genetic diseases? Does the cell or tissue processing pose a risk of contamination or damage? What are the types of cells, and what are the purity and potency of the cells in the final product? Will the product be safe and effective *in vivo* [9]? Initially, one of the foremost considerations must be the cell types. By 2013, a search of www.clinicaltrials.gov, a US government-sponsored website, with the term ''stem cells'' lists almost 2000 trials. The relative ratio of open trials approved for different stem cell types is listed on clinicaltrials.gov, which indicates a wide range of stem cell types are being applied to clinical trials (Figure 2).

2.1 Hematopoietic stem cells (HSCs)

HSCs are multipotent cells that reside in the bone marrow, peripheral blood, placenta, and other tissues that sustain the hematopoietic system. Accumulated literature has confirmed that HSCs are able to reconstitute the hematopoietic system in disease-related bone marrow failure and bone marrow aplasia. In fact, apart from HSC transplantation, essentially all other stem cell treatments remain experimental or preclinical [10]. Currently, the majority of clinical trials aim to build on decades of research and clinical experience in hematopoietic transplantation. New strategies include expansion of suboptimal numbers of HSCs within umbilical cord blood, correction of gene defects in HSCs through viral transgene delivery, and engineering T cells to attack malignancies via adoptive immunotherapy [11,12]. Despite the relatively poor understanding of the therapeutic mechanisms, other stem cells, such as mesenchymal, adipose-derived, and neural stem cells, are being tested innumerous animal experiments and clinical trials.

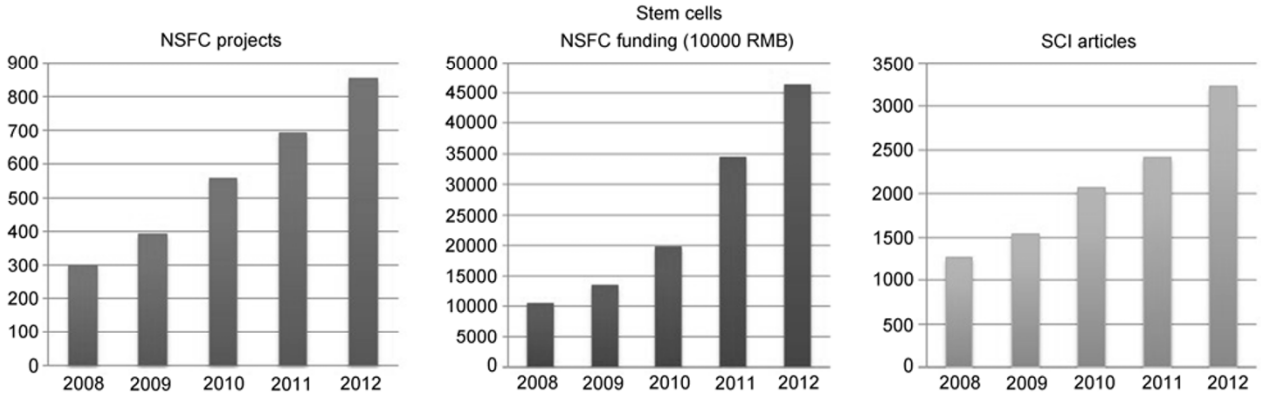

Figure 1 Approved projects and funding from the NSFC and related published articles on stem cell-based research and trials from 2008 to 2012.

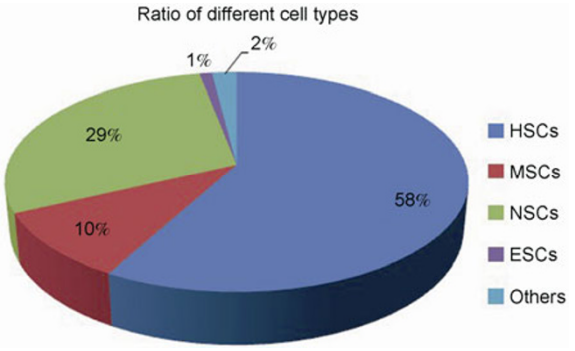

Figure 2 Pie chart of major stem cell types in clinical trials. The relative ratios of approved trials for hematopoietic, neural, mesenchymal, embryonic and other tissue-derived stem cells as listed on the US National Institutes of Health website, clinicaltrials.gov.

2.2 Mesenchymal stem cells (MSCs)

MSCs are usually derived from bone marrow but can be isolated from adipose and other tissues. They are defined by their fibroblast-like morphology and capacity for osteogenic, chondrogenic, and adipogenic fates *in vitro* [13]. MSCs have also been reported to regenerate functional sweat glands, which may help to solve the problem of sweat gland depletion in patients surviving extensive deep burns [4]. Easy access to large quantities is an advantage of adipose-derived stem cells that are being tested for soft-tissue repair and regeneration. Both autologous and allogeneic MSCs are being evaluated *in vivo* to improve healing that reflects their *in vitro* potential to form bone or cartilage for use in bone fracture and joint cartilage repair [14]. Although such studies appear to indicate strong evidence and sound scientific hypotheses, evidence for the robust clinical efficacy of MSCs for orthopedic indications has been challenging to confirm. To date, no therapy based on MSCs has been approved by the FDA. The difficulty in proving therapeutic efficacy based on the well-characterized potentials of MSCs suggests that our understanding of how even familiar stem cells can be used therapeutically *in vivo* remains poor.

Furthermore, although MSCs are being tested in a wide range of clinical indications, their therapeutic mechanisms are not defined completely, and in some cases, the preclinical evidence is highly contentious [15]. At the same time, the clinical application of MSCs continues to increase markedly. Recently, numerous studies have revealed a variety of mechanisms including paracrine effects, neoangiogenesis, and biomechanical alterations because of scarring [16–18]. Moreover, MSCs have been widely tested for their capacity to mitigate autoimmunity. MSC-mediated tissue regeneration has undergone considerable evolution. Unfortunately, the remarkable advancements in basic stem cell research with implications have so far not been translated into clinically effective therapies.

2.3 Umbilical cord blood stem cells (UCBSCs)

The umbilical cord is a rich source of HSCs that can be easily extracted and cryopreserved, and used to reconstitute the blood system, thus allowing establishment of human leukocyte antigen-typed stem cell banks. However, controversy exists concerning whether cord blood can serve as a source of MSCs that can differentiate into cells of different connective tissue lineages such as bone, cartilage, and adipose. Little success has been reported in the literature regarding the isolation of such cells from cord blood [19]. Recently, umbilical cord blood has emerged as a viable alternative to other sources of HSCs for the treatment of leukemia and nonmalignant hematologic conditions [20]. It has also become a common source for experimental interventions in a wide variety of nonhematological indications as disparate as myocardial infarction, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, traumatic brain injury, stroke, and inherited metabolic disorders [21–24]. While UCBSCs can mediate therapeutic effects in theory, nonhematological indications for UCBSC transplantation have not been widely accepted in standard practice. Without a deeper understanding of their basic therapeutic mechanisms, it is difficult to implement therapeutic strategies and clinical investigations on a large scale.

2.4 Neural stem cells (NSCs)

NSCs can be obtained from fetal and adult brain, and have been demonstrated to differentiate into neurons, oligodendrocytes, and astrocytes *in vitro*. Considering the wide range of neurological conditions that have devastating clinical consequences, there is remarkable interest in the therapeutic potential of neural regeneration. However, stroke, traumatic brain injury, spinal paralysis, and neurodegenerative diseases are among the most daunting challenges for regenerative medicine. There are hundreds of clinical trials in academic settings and those performed by several companies to develop novel therapies through intracerebralor spinal transplantation of NSCs [25]. StemCells Inc. (Irvine, California, USA) has tested NSCs in Batten's disease (neuronal ceroid lipofuscinosis), and documented safe delivery but discontinued the trial because of the inability to accrue an adequate number of patients. Their current focus is Pelizaeus-Merzbacher disease, a myelin disorder, and chronic spinal cord injury. Other companies are testing NSC transplantation for stroke (ReNeuron, UK), amyotrophic lateral sclerosis (Neuralstem, Inc., USA), and Parkinson's disease (NeuroGeneration, USA). In most cases, the clinical implications being tested do not depend on the generation of neurons, but on complementation of enzyme deficiencies, remyelination, or modulation of endogenous repair through neoangiogenesis or neuroprotection.

2.5 Embryonic stem cells (ESCs)

In theory, ESCs are pluripotent because they show the capacity to generate every type of cell and tissue of the body [26]. However, there are comparatively few clinical trials of

products derived from ESCs. For example, current clinical trials involve human ESC-based interventions for retinal blindness. The retina is accessible for local cell delivery, which can be monitored by direct visualization. In addition, the retina may provide a certain degree of immune privilege. Despite only one patient in each trial, subretinal injection of human ESC-derived retinal pigment epithelial cells has been applied to Stargardt's macular degeneration and age-related macular degeneration, which were sponsored by Advanced Cell Technologies (Marlborough, USA) [27]. Only one of the two patients showed evidence of persistent cells but both patients showed some restoration of visual perception. Because of the limited numbers of patients involved and the very brief period of follow-up (4 months), it is difficult to draw conclusions from these early trials. Nevertheless, the trials are milestones because investigators succeeded in clearing considerable regulatory hurdles and met very high standards of preclinical cell characterization and quality control prior to exposing patients to the risk of products derived from ESCs.

While MSCs, NSCs, and ESC-based products are being tested in numerous clinical trials, tissue engineering, as another arm of regenerative medicine, is particularly appealing. The potential for therapeutic innovation of stem cell biology and tissue engineering represents a solution for the medical needs of specific patients as acceptably performed and highly innovative and individualized therapies. Taken together, development of such novel therapies, sound scientific rationale and methods, institutional and practitioner accountability, thorough and rigorous informed consent, patient follow-up, timely reporting of adverse events, peer review of therapeutic claims, and publication in medical literature are indispensable and meaningful.

3 Barriers and challenges

The maturation of a new therapeutic approach requires decades, and stem cell-based therapy is no exception. A major problem hindering the development of these new therapeutics, in our opinion, is insufficient translation of basic research findings to patients. In many settings, the clinic and the basic research laboratory are often completely different. Basic and clinical scientists, as well as scientists working in the biotechnology and pharmaceutical industries, need increased awareness of the questions that must be answered before a stem cell-based product can be used clinically. Unlike pharmaceutical products, many stem cell-based products may originate from academic laboratories where researchers are unfamiliar with the applicable regulations. For clinical efficacy, clinicians have to be involved from an early stage of basic stem cell research and not just immediately before application to patients [28]. Furthermore, basic scientists should acknowledge the clinical problems related to the diagnosis and therapy of diseases. The partnership between basic scientists and clinicians must function throughout all stages of clinical translation if basic research findings are to be efficiently converted to novel treatments. Hence, based on our multidisciplinary teams and multimodal approaches, we recently established a specialized biological treatment ward at our hospital for efficient clinical translation. Moreover, successful clinical translation of stem cells will depend on not only the right type of cell, but also an appropriate site for cell delivery as well as suitable patients [28–30].

Other barriers to applying stem cell-based treatments are the high costs and uncompetitive business development. For effective clinical translation, scientists should perform health economic studies at an early stage to estimate the potential value of further research in stem cell therapy for various disorders to ensure the best use of research investments. Translation of discoveries in basic stem cell research into safe and effective clinical products will be very expensive. The estimated costs of stem cell therapies will be important for companies and scientific institutions manufacturing stem-cell-based products [31]. In the US, the transition from discovery to therapy usually involves profit entities. Several companies have made discoveries, obtained preclinical proof of principle, and even performed phase I/II clinical trials in the stem cell field. Unfortunately, domestic companies developing stem cell-based products are rather lacking. Even estimating the cost of stem cell therapy by health economics modeling is uncommon in China [32]. Despite significant research funding provided by the government, it is far from enough. This current situation may further delay the development of clinically effective stem cell therapies in China.

The most significant hurdle that remains for stem cell therapies is unproven therapies without regulation. Administering interventions outside of controlled trials threatens patients and harms the integrity of public trust in medical research [33]. Because of the particular vulnerabilities of patients, many governments have established laws to protect patients from risk, but some medical practitioners regard the regulations as a burden and constraint on their trials [34]. Recently, the German government shut down the Xcell Clinic when a child died after receiving unproven intracranial injections of cord blood. While most stem cell interventions are documented to have no side effects, safety issues still require attention [35]. To advance clinical investigation and promotion of medical innovation while protecting patients and ensuring integrity in regenerative medicine, the International Society for Stem Cell Research (ISSCR) assembled an international group of scientists, surgeons, genetherapists, bioethicists, patient advocates, and attorneys to create ''The ISSCR Guidelines for the Clinical Translation of Stem Cells'' [36]. These guidelines articulate principles and standards as a guide for practitioners and regulatory bodies when considering if, when, or how to allow trials of experimental stem cell therapies in patients. The reliability of the preclinical evidence for efficacy and safety of stem cell-based products and rigorous decisions by those who are free of conflicts of interest are essential for considering the potential risks against the potential benefits before launching a clinical trial.

4 Conclusion

Translation of the basic discoveries of stem cell biology into effective and safe therapies will overcome numerous challenges and technical barriers. Before success, stem cell-based regenerative medicine will suffer many setbacks. Although the challenges of stem cell application are complex and should not be underestimated, the development of novel stem cell-based therapies will benefit greatly from experience and failures as well as increasing support. We hope that the new field of regenerative medicine can advance by solving challenges effectively.

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